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Exploratory Psychometric Validation and Efficacy Assessment Study of an Agoraphobia Treatment based on Virtual Reality Serious Games and Biofeedback

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I hear you on the horizon
the epiphanies of a rising desire
I feel your magnificent sound waves
purring from the depths of a heartbeat
I know that music well
it is the magic that transcends
and lifts with the light of day
in symphonic colors of life
Shilow

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ABSTRACT

Current treatment methods for mental disorders – namely, psychotherapy and pharmacology – have several limitations. Specifically, phobias' treatment lack quantification, personalization to the patient, a gradual and controlled therapy pace, and safety, since it relies on *in vivo* exposure therapy (phobic desensitization). Research has shown the efficacy of using virtual exposure therapy, based on Virtual Reality (VR) serious games. However, although this method enables a gradual and controlled therapy pace, it does not solve quantification and personalization. Thus, the hypothesis to add biofeedback – an emergent technique that uses vital signs to directly control a system's adaptation, widely used for brain training systems – to personalize and quantify virtual exposure therapy, arose. This study aims to assess the efficacy of a novel agoraphobia (extreme anxiety/fear of crowded open or closed spaces) treatment method based on VR serious games and biofeedback, as a complement to the conventional methods. The addition of a complementary VR relaxation technique – following the phobic exposure – was also studied. As a first step, the study aims at evaluating if anxiety elicits differentiated brain and heart activity responses, i.e., it aims at evaluating if anxiety biomarkers can be retrieved.

Following previous research, a preliminary study was conducted with 156 healthy subjects that watched a set of videoclips that elicited different emotional responses, while their brain and heart activity was monitored through Electroencephalography (EEG) and Photoplethysmography (PPG) sensors, respectively. The fear/anxious emotional category elicited differentiated responses on heart and brain activity, suggesting that certain features can be used as anxiety biomarkers. It was retrieved conclusions regarding the best anxiety biomarker performer, showing the strongest correlations with the self-reporting emotional states, suggesting that the Anxiety/Fear emotional state elicited most differentiated responses on the cardiovascular system, rather than on the Central Nervous System and providing insights into the not yet consensual literature on the topic.

Then, a proof-of-concept trial of 8 sessions was conducted with 5 agoraphobic patients, in which 3 of them underwent the conventional treatment protocol with the addition of the novel VR + biofeedback method, while the other 2 only underwent the conventional protocol. The novel method's protocol begins with agoraphobia and anxiety self-assessment questionnaires, then moves to the VR phobic exposure scenario, and, lastly, to the VR relaxation scenario. Results showed that the decrease of anxious and agoraphobic symptoms, between the initial and last sessions, in the experimental group was *3.28* and *5.02* times greater, respectively, than the decrease of those symptoms in the control group. Results regarding anxious and relaxed states' biomarkers were also retrieved. Overall, these findings show and quantify the added-value of this novel therapy method – innovative in the literature –, as a complement to the conventional psychotherapy, showing that, as hypothesized, the mixed exposure + relaxation approach enables a more significant symptom reduction. Future work will assess the efficiency and added-value of biofeedback, using Machine Learning methods, as well as of a home-based approach.

Keywords: *Virtual Reality Exposure Therapy; Agoraphobia; Biofeedback, Emotion Recognition; Digital Health*

RESUMO

Uma fobia é um tipo de perturbação ansiosa, definida por um medo persistente e excessivo em relação a um objeto ou situação, tendo um impacto bastante limitativo na vida do doente fóbico. Atualmente, as perturbações mentais são ainda vistas como tabu, e existe uma elevada incidência de pessoas que sofrem de fobias (~ 83M na União Europeia, e 32M no Estados Unidos da América).

Os métodos atuais para tratamento de perturbações mentais baseiam-se sobretudo em psicoterapia e em farmacologia. Especificamente, o tratamento de perturbações fóbicas baseia-se em terapia por exposição *in vivo.* Esta técnica foca-se em alterar a resposta do doente ao objeto ou situação que é alvo de medo, através de exposição repetida ao mesmo. A título de exemplo, um doente de fobia de elevadores pode iniciar a sua terapia apenas a pensar em entrar num elevador. De seguida, o terapeuta pode levar o doente a andar de elevador apenas de um andar para o seguinte, a andar de elevador durante vários andares, e a entrar num elevador muito lotado. Este método designa-se assim por dessensibilização fóbica.

No entanto, os métodos convencionais possuem várias limitações. Nomeadamente, o tratamento de fobias peca pela falta de quantificação (não são retiradas quaisquer métricas de avaliação), personalização ao doente (a personalização é apenas dependente da opinião subjetiva do terapeuta), ritmo terapêutico gradual e controlado, e segurança, visto que se baseia em terapia por exposição *in vivo*.

A investigação tem demonstrado a eficácia da utilização alternativa de terapia por exposição virtual, baseada em jogos sérios em Realidade Virtual (RV). No entanto, apesar deste método permitir um ritmo terapêutico gradual e em segurança (permitindo uma exposição fóbica virtual no ambiente clínico seguro, ao invés de in vivo – em estágios terapêuticos iniciais e intermédios), não soluciona a falta de quantificação e personalização. Assim, surgiu a hipótese de adicionar *biofeedback* – uma técnica emergente que utiliza sinais vitais para controlar diretamente a adaptação de um dado sistema, amplamente aplicada em sistemas de treino cerebral – para personalizar e quantificar a terapia por exposição virtual. A técnica é bastante utilizada recorrendo a sinais cerebrais (Neurofeedback), no entanto também são utilizados sinais cardiovasculares, por exemplo.

É atualmente conhecido que, a nível fisiológico, as emoções (especificamente o medo) e a ansiedade são correlacionáveis com respostas fisiológicas do sistema cardiovascular. Por exemplo, o sistema cardiovascular responde ao stress, em conjunto com o sistema endócrino, com elevados níveis de cortisol e com um ritmo cardíaco e uma pressão sanguínea aumentados.

O presente estudo avalia a eficácia de um novo método de tratamento de agorafobia (ansiedade/medo extremos de espaços abertos ou fechados com multidões) baseado em jogos sérios em RV e *biofeedback*, como complemento aos métodos terapêuticos convencionais. A adição de uma técnica complementar de relaxamento em RV – seguinte à exposição fóbica – é também avaliada. Como primeiro passo, o estudo avalia se a ansiedade suscita respostas cardíacas e cerebrais diferenciadas, isto é, se é possível retirar biomarcadores da ansiedade.

Seguindo investigação prévia, uma experiência preliminar foi conduzida com 156 pessoas saudáveis que assistiram a um conjunto de videoclipes que suscitavam respostas emocionais diferentes, enquanto que as suas atividades cerebrais e cardíacas foram monitorizadas através de sensores de Eletroencefalografia (EEG) e Fotopletismografia (PPG), respetivamente. Foram estudadas seis categorias emocionais: Medo, Alegria, Raiva, Nojo, Neutro, Tristeza, e Ternura. A categoria emocional de Ansiedade/Medo suscitou respostas diferenciadas nos sinais fisiológicos, sugerindo que componentes podem ser utilizadas como biomarcadores da ansiedade. A categoria emocional Ternura foi também

alvo de uma análise detalhado, dado que esta é uma emoção ainda pouco conhecida, não sendo consensual a sua natureza.

De seguida, um teste de prova-de-conceito de 8 sessões foi conduzido com 5 doentes de agorafobia, dos quais 3 deles foram submetidos ao protocolo terapêutico convencional com a adição do novo método de RV + *biofeedback*, enquanto que os restantes 2 doentes foram submetidos apenas ao protocolo convencional (psicoterapia e farmacologia). O protocolo do novo método inicia-se com questionários de auto-avaliação de agorafobia e de ansiedade, de seguida passa para o cenário RV de exposição fóbica, e finalmente para o cenário RV de relaxamento. O cenário RV de exposição fóbica consiste numa sala de cinema, na qual o número de pessoas varia de sessão para sessão consoante os resultados fisiológicos e auto-reportados do doente na sessão anterior (*biofeedback* manual). Por outro lado, o cenário RV de relaxamento consiste numa praia paradísica numa ilha, na qual a turbulência das ondas do mar varia automaticamente consoante os resultados fisiológicos e auto-reportados do doente na sessão anterior (*biofeedback* preliminar).

O objetivo do cenário RV de exposição fóbica é assim expor o doente gradualmente ao cenário de fobia, personalizando o nível de exposição em cada sessão consoante a sua resposta, através do *biofeedback*. Ou seja, se na sessão anterior o doente conseguiu estar confortável no cenário, o que se traduz nos seus sinais fisiológicos, na sessão seguinte é exposto a um cenário de maior intensidade, obrigando-o assim a habituar-se gradualmente ao cenário. Contrariamente, o objetivo do cenário RV de relaxamento é relaxar gradualmente o doente, expondo-o a um cenário cujo caráter relaxante se intensifica à medida que o doente relaxa, seguindo uma metodologia de *biofeedback* semelhante.

Os resultados mostraram que a diminuição dos sintomas ansiosos e agorafóbicos, entre a primeira e a última sessões, no grupo experimental, foi *3,28* e *5,02* vezes mais elevada, respetivamente, do que a diminuição desses sintomas no grupo de controlo. Resultados relativos a potenciais biomarcadores de estados ansiosos e relaxados foram também adquiridos. De um modo geral, estas conclusões sugerem e quantificam o valor acrescentado deste novo método terapêutico, como complemento à psicoterapia convencional, demonstrando, como foi conjeturado, que a abordagem mista de exposição fóbica + relaxamento permite uma maior redução sintomática.

O presente trabalho constitui assim um avanço no estado-da-arte, dado que se retiraram resultados conclusivos relativamente à eficácia e valor acrescentado de um método terapêutico inovador, ainda não explorado na literatura.

Trabalho futuro irá avaliar a eficácia e o valor acrescentado do *biofeedback*, através de um grupo de controlo com *biofeedback* placebo. Os jogos sérios poderão também ser melhorados, desenvolvendo outros cenários e também os triggers da ansiedade, alvo do controlo automático via biofeedback. Pretende-se também otimizar o *biofeedback*, através de algoritmos de Aprendizagem Automática de reconhecimento emocional, nomeadamente utilizando algoritmos de redes neuronais. Especificamente, o presente trabalho servirá de base para o desenvolvimento e avaliação de um classificador de estados ansiosos baseado nos biomarcadores encontrados. Por fim, planeia-se ainda avaliar o valor acrescentado de uma abordagem terapêutica no domicílio, como complemento à terapêutica clínica.

Palavras-chave: *Terapia de Exposição por Realidade Virtual; Agorafobia; Biofeedback; Reconhecimento Emocional; Saúde Digital*

COMMUNICATION OF INVENTION AND CONFIDENTIALITY

The present research work resulted in the creation of an invention submitted to the Board of the Faculty of Sciences of Lisbon University in the form of an *"Communication of Invention"*, as it is recommended to occur in these cases.

The *"Communication of Invention"* was accepted by the Faculty of Sciences' Board *[Appendix I]*, which then began the bureaucratic process that was recently translated in the creation of a new faculty's spin-off company, *NevaroTech Lda.*

Furthermore, given that the present research work includes know-how owned by the company, it is a **confidential** piece of work. Hence, it can only be accessed with permission.

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1. Introduction

On this chapter I introduce the motivation and background behind the research work, on a very personal note. I also introduce a overview of the entire research work, chapter by chapter.

I wish to highlight that the present research work is a collaboration between several people and me, without whom it would not have been possible: Rita Maçorano (MIEBB, FCUL), Rafael Ramos (MIEBB, FCUL), prof. Dr. Hugo Ferreira (IBEB/FCUL), prof. Dr.ª Ana Paula Boler Cláudio (DI/FCUL), prof. Dr.ª Beatriz Carmo (DI/FCUL), Dr.ª Ana Matos Pires (ULSBA, Beja), and Dr.ª Maria Suárez Goméz (ULSBA, Beja). The project is also supported by IBEB, *TecLabs* (innovation center based at FCUL), and the startup *EmotAI*.

1.1. Motivation and Background

The present research work consists of my master thesis project, developed over the past year.

I will start to explain the motivation behind this work. The idea behind it started two years ago, while starting my master's degree in biomedical engineering and biophysics (MIEBB), in a neurosciences course lectured by professors Alexandre Andrade and Hugo Ferreira, at the Faculty of Sciences of the University of Lisbon (FCUL). On that course, me and my colleagues (Rita Maçorano, Silvestre Piedade, and, later on, Rafael Ramos) started the research and development behind the present work.

After the course, Rita and I decided to continue that work on our master thesis. At the time, I was already starting my master thesis at *Champalimaud Foundation*, Lisbon. However, this research field caught my interest since it combines subjects that I am enthusiastic about, namely psychology, neurosciences, medicine, biomedical engineering, and technology. Understanding and discovering the human brain and behavior has always been one of my interests, and, in the last years, I have been developing a passion for personal development, self-discovery and self-growth, and emotional intelligence. Therefore, I am particularly interested in exploring these fields, which are intimately connected with the present research work, from a scientific and analytical perspective.

Hence, at that time, I was presented with a hard choice: pursue the *Champalimaud Foundation* project – a reference research institute in neurosciences - or take a leap of faith and pursue our research project. Passion, intuition, faith, and purpose won. I left *Champalimaud* and started my master thesis project at the Institute of Biophysics and Biomedical Engineering (IBEB), at FCUL, under the supervision of professors Hugo Ferreira and Ana Paula Cláudio.

Besides that very personal motivation, the present research work was also motivated by the awareness to the topic of mental healthcare, specifically by its limitations. Building upon previous research and projects developed on the course of my master's, the motivation to use biomedical technology to improve mental healthcare arose.

The present research work is in fact focused on the digitalization of mental healthcare, as a complement to the conventional methods. Specifically, it is focused on developing, studying, validating, and deploying an agoraphobia treatment based on Virtual Reality and biofeedback, as follows in the next chapters.

1.2. Overview

Chapter 2 (Literature Review) contains a review of the existing literature, in order to reach a state-of-art conclusion concerning the topic. This preliminary work serves as a guideline to the dissertation plan, providing the necessary background to hypothesize what should be studied and to pinpoint the aimed contribution to that aspect, and therefore to take a small step in the research regarding mental disorders treatment.

Based on that, on *Chapter 3 (Dissertation Plan)* it is defined the proposed research hypothesis and the corresponding study goals. Then, there is described the planned work timeline, including the milestones for each stage and the respective work methods and protocols.

Chapter 4 (Theoretical Background) introduces and discusses the theoretical subjects regarding the topic, which practical application is then described on *Chapter 5 (Materials and Methods)*. On *Chapter 6 (Results and Discussion*), the obtained results are presented and discussed.

Chapter 7 (Conclusions) is firstly dedicated to correlate the initial hypothesis with the results, and to withdraw conclusions, as well as to assess those conclusions' validity. Additionally, the retrieved conclusions are compared with the ones from the state-the-art, described on *Chapter 2*, in order to analyze the broader panorama of the topic. Finally, the chapter includes some final words about the research work: from its limitations to a description of further improvements and future work, to a personal reflection section – regarding the team's achievements and the business perspectives, as well as a personal outlook and balance of the research work.

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APPENDICES

Appendix I - *"Communication of Invention"* submitted to the Board of the FCUL

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Processo: 4/2018

Comunicação de invenção: NEVARO

Proponentes: Francisca Canais, Rita Maçorano, Silvestre Piedade e Rafael Ramos

Data: 17 de janeiro de 2019

Tendo por base a análise da comunicação de invenção submetida em 02/11/2018, as reuniões informais efetuadas com os proponentes e a reunião efetuada em 05/12/2018 com o Prof. Hugo Ferreira, na dupla qualidade de especialista no tipo de tecnologia em questão e de orientador das dissertações de mestrado de Francisca Canais e Rita Maçorano, relevam os seguintes pontos:

a) A comunicação de invenção identifica os inventores, descreve de forma detalhada a tecnologia desenvolvida, faz a descrição do estado da técnica, identifica a novidade introduzida em relação ao mesmo, e identifica a divulgação que já foi feita da tecnologia (documentos anexos), nomeadamente em programas de promoção do empreendedorismo e financiamento de *start-ups*;
b) A tecnologia apresentada na comunicação de invenção encontra-se na fase de *Small Scale Prototype (TRL 4);*
c) Existem outras soluções no mercado para a mesma finalidade (terapia de fobias) da tecnologia desenvolvida, mas que não incorporam as três componentes que a tecnologia NEVARO incorpora, nomeadamente a componente neuro. O produto desenvolvido é ainda inovador pela integração conjunta da *headband*/dispositivo de visualização;
d) A tecnologia NEVARO carece ainda de uma fase crucial de teste e validação, sendo que parte desse trabalho será desenvolvido no âmbito das dissertações de mestrado de Francisca Canais e Rita Maçorano, sob orientação do Prof. Hugo Ferreira;
e) Na comunicação de invenção é referido pelos inventores o interesse em proteger a tecnologia desenvolvida como patente, através da submissão de um Pedido Provisório de Patente;
f) Os inventores pretendem criar a sua própria empresa (*spin-off*) e simultaneamente desenvolver mais contactos com a indústria do setor.

Analisada a comunicação de invenção, esclarecidos alguns aspetos no decorrer das reuniões efetuadas com os inventores, e ouvido o Prof. Hugo Ferreira, a FCUL considera prematura a submissão de um pedido provisório de patente, que teria um tempo de vida útil máximo de 12 meses, findo o qual seria necessário converter em pedido definitivo (nacional ou internacional), com os custos inerentes e imediatos, ou em alternativa abandonar o pedido provisório de patente, o que significa que não se ganha tempo em termos de reivindicação da prioridade.

Nestas circunstâncias considera-se que o mais adequado é esperar pelos resultados da fase de teste e validação da tecnologia, que já está a decorrer, e que poderá conduzir a resultados relevantes.

Considera-se ainda que deverá ser avaliado periodicamente, em função dos resultados que forem sendo produzidos, e em estreita colaboração com os inventores e com o Prof. Hugo Ferreira, o melhor momento para a submissão do pedido provisório de patente.

Ciências ULisboa

Jorge Maia Alves

Subdiretor

Figure I.1 - "Communication of Invention" submitted to the Board of the FCUL